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10/553,614	10/18/2005	Mitsuharu Hirai	TOYA114.009APC	4647

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EXAMINER	
BAUGHMAN, MOLLY E	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
06/07/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/553,614	HIRAI, MITSUHARU	
	Examiner	Art Unit	
	Molly E. Baughman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's arguments filed 3/12/2007, with respect to rejection(s) of claim(s) 1-9 have been fully considered but they are not persuasive for reasons explained in detail below.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (WO 02/072875 A1) in view of Crockett et al. (2001).

Regarding claims 1-3, Lee et al. describe the use of a combination of mutated gene sequences from wild-type genes that are involved in insulin secretory function, one of which is S20G amylin (page 4, Summary of the Invention, 1st paragraph). Sequence ID NO:12, shown in Figure 5, is the nucleic acid sequence of the human amylin gene exon 3 with the S20G mutation (Brief Description of the Drawings, page 6), which comprises the nucleotide at nucleotide number 247 and a sequence 5' to the nucleotide in the nucleotide sequence of SEQ ID NO:1 of the instant invention [claim 1], as well as comprising the corresponding nucleotide sequences of SEQ ID NO: 12 and 13 [claim 2]. Lee et al. describe that "the nucleic acid probes of the invention are

nucleic acid sequences from the mutated genes of interest. They are at least 8, 12, 15 or 20 base pairs in length, but can be 50, 80 or 100 base pairs in length, and include at least one associative mutation but may include multiple mutations and can be as long as the length of the transcribed gene" (page 14, last paragraph) [claim 1]. In one embodiment, a method comprises contacting a sample with a representative combination of at least two mutated genes of interest, subjecting the DNA to hybridization to detect nucleotide differences of at least one base pair (page 4, Summary of the Invention, 2nd paragraph). This can be done by attaching the mutated genes of interest to a microchip or other solid support (page 5, 2nd paragraph).

Lee et al. do not describe a probe comprising the 5' end labeled with a fluorescent dye, and in which fluorescence of the fluorescent dye decreases upon hybridization [claim 1]. They also do not describe a method for detecting a mutation comprising performing a melting curve analysis for a nucleic acid having a single nucleotide polymorphism site by using a nucleic acid probe labeled with a fluorescent dye and measuring fluorescence of the fluorescent dye, and detecting the mutation on the basis of a result of the melting curve analysis [claim 3].

Crockett et al. describe a method of using a single 5'-fluorescein probe in real-time PCR for quantification and genotyping. In their method, amplification was accompanied by a decrease in fluorescence corresponding to PCR product accumulation (page 90, results, and Figure 1B). They note that instead of an increase of fluorescence with increasing product concentration, quenching results in a decrease in fluorescence (page 93, 2nd column, 1st paragraph). In their studies, they analyzed

varying the content and placement of specific nucleotide resides, particularly Cs complementary to Gs in the target sequence, within the probes in correlation to the placement of the fluorescein (page 91). Using the information obtained from their modeling systems, they were able to design probes which optimized quenching during hybridization to analyze several polymorphisms within genes (pages 92-95). Their analysis concluded that "the extent that a fluorescein-labeled probe is quenched by deoxyguanosine nucleotides on the complementary unlabeled strand depends on the position and dose of opposing G residues" and furthermore, "the first dangling base on the unlabeled strand should be a G" (i.e. the 5' labeled nucleotide should be a C) (page 95, 1st column, 2nd paragraph).

In genotyping assays of Crockett et al. using specifically designed fluorescein-quenching probes, homozygotes complementary to the probe melt at a relatively high temperature, homozygotes that are mismatched to the probe melt at a relatively low temperature (page 92, 1st column, first paragraph). In one assay, when genotyping hemoglobin mutations, they designed a probe homologous to the hemoglobin S sequence, which covered the polymorphic site and the fluorescein was placed opposite to two G residues (page 92, 2nd column, 1st paragraph, and Figure 6 description). They also discuss genotyping hemoglobin C and S mutations with a probe that has a 5' C which hybridizes opposite to two Gs (Figure 6, A). The probe was included in the PCR amplification mixture with primers targeting the polymorphic region and Klen-Taq polymerase, and melting curve analysis was automatically performed after PCR (Figure 6 description). By using slow heating during the reaction, "a 'dynamic dot blot' is

produced that identifies alleles by their melting temperature (page 94, 2nd column, first paragraph). "Derivative melting curves easily distinguish different genotypes by quenching from one (Figs. 7 and 8) or two (Figs. 5 and 6) Gs" (page 94, 2nd column, first paragraph).

Regarding claims 4-6, Lee et al. also discuss PCR analysis using primers designed to anneal to the wild-type gene sequence in regions that flank the mutation in a gene of interest (page 15, last paragraph). In Example 3, page 41, DNA fragments spanning the mutation site of S20G of the amylin gene were amplified by PCR using primers of SEQ ID NO:30 and 31.

Regarding claims 7-9, Lee et al. also discuss a kit comprising a solid support having attached to it a representative array of nucleic acid sequences, each with a mutation or polymorphism associated with the genetic disposition (page 4, paragraph [0032]). The microassay kit with nucleic acid sequences immobilized on a solid support would involve screening by hybridization detection (fluorescent or radioactive signal upon duplex formation). Alternatively, the kit would include primer pairs that anneal to the nucleic acid sequences encoding proteins involved in insulin secretion. The primer pairs specifically anneal to flanking regions of the genes that putatively contain mutations associated with type 2 diabetes (page 4, paragraph [0032]).

Lee et al. do not discuss a kit comprising a probe comprising its 5' end labeled with a fluorescent dye, and in which fluorescence of the fluorescent dye decreases upon hybridization.

The teachings of Crockett et al. are discussed above, including the instant claims 7-9, using a single 5'-fluorescein probe specific for a single nucleotide polymorphism which decreases in fluorescence upon hybridization.

One of ordinary skill in the art would have been motivated to modify the method of Lee et al. to use a fluorescein which decreases in fluorescence upon hybridization to label the probe and use the labeled probe in a melting curve analysis to detect the mutation because not only do Crockett et al. demonstrate the ability to design singly labeled 5' fluorescein probes that optimize quenching during hybridization to specific targeted polymorphisms, they also state that "fluorecein quenching probes are very easy to design, synthesize, and use in real-time PCR applications. They are more specific than double-strand DNA dyes like SYBR Green 1 and, unlike other internal probes, do not require the synthesis of a quencher on the same molecule," and furthermore, "single-labeled fluorescein probes provide a simple means of probe-based quantification and allele typing" (page 96, last paragraph). The skilled artisan would have had a reasonable expectation of success in labeling the probe of Lee et al. with a fluorescein which decreases in fluorescence upon hybridization, use the labeled probe in a melting curve analysis to detect the mutation, and include it in their kit. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use the claimed probe and label it with a fluorescein which decreases in fluorescence upon hybridization, and use it in a melting curve analysis for mutation detection therein.

Response to Arguments over Rejection under 35 U.S.C. 103(a) (Lee et al. (WO 02/072875 A1) in view of Crockett et al. (2001)).

3. Applicant's arguments filed 3/12/2007, with respect to rejection(s) of claim(s) 1-9 have been fully considered but they are not persuasive. Applicants argued that Lee et al. do not specify the nucleotide at number 247 and do not recognize that the nucleotide number 247 should correspond to the 5' end of any probe, however, the claim as written do not require such limitations. Claim 1 and 7 do not require the 5' end of the probe to correspond to the nucleotide at nucleotide number 247 and only requires the probe to comprise the nucleotide at nucleotide number 247 and sequence 5' to the nucleotide in the nucleotide sequence SEQ ID NO:1, where such limitations are met by Lee et al. Lee et al. state that the probes are at least 8, 12, 15 or 20 base pairs in length and cover the mutation of interest, including the instant S20G mutation and further state that the probes are labeled with fluorescers for detection (pg. 6, [0041]).

Second, Applicants argue that Lee et al. do not specifically discuss the fluorescent dye decreasing upon hybridization, and Crockett et al. do not teach the quenching probes of the invention. As discussed above, Crockett demonstrates, one of skill in the art would have designed such a probe through routine experimentation. Crockett specifically demonstrates that probes designed with one or two Cs at the 5' end, opposite to two G nucleotides in the target sequence, particularly wherein one C nucleotide is hybridized to one of the two G nucleotides and the second G nucleotide is directly 5' and outside the sequence of the probe, the quenching is maximized and specific mutations can be detected. Crockett's preferred design correlates to the probes

of SEQ ID NO:12 and 13, which comprise one C nucleotide at the 5' end and hybridize to the target sequence which has two Gs, one of which is hybridized to the probe and the other is directly 5' and outside the sequence of the probe and therefore, the skilled artisan would have expected successful quenching in such a probe as taught by Crockett. As Crockett demonstrates, one of skill in the art would have expected that the cytosine complementary to guanine nucleotide at nucleotide number 247 of SEQ ID NO:1 would be critical to maximum fluorescence and that probes having a cytosine end but complementary to guanine at positions other than position 247 would not produce the expected changes, because the guanine at nucleotide number 247 is directly adjacent to another guanine in SEQ ID NO:1 and the other probes with 5' cytosines complementary to other guanines do not have neighboring guanines, which Crockett demonstrates is critical for designing a probe that will produce the maximum fluorescence quenching when hybridized (see Figure 4 and 5). Therefore, one of skill would have been motivated to designed the probes of Lee et al. to have a 5' cytosine and complementary to guanine at nucleotide number 247 and would have had a reasonable expectation of success in using such probes to detect the S20G mutation upon results of Tm analysis since Crockett demonstrates that such designed probes are useful in detecting mutations and "are free of some previously described artifacts of other probe designs that appear with extensive temperature cycling" (pg.93, 2nd paragraph).

SUMMARY

4. No Claims are free of the prior art.

CONCLUSIONS

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is 571-272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Molly E Baughman
Examiner
Art Unit 1637

MEB 5/30/07

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

5/30/07